II. REMARKS

Introductory Comments

Claims 1, 6-8, and 13-15 were examined in the Office Action under reply and stand rejected under 35 U.S.C. §103(a). This rejection is respectfully traversed for reasons discussed in detail below.

Applicants note with appreciation the withdrawal of the previous rejections under 35 U.S.C. §112, first and second paragraphs, as well as the previous rejection under 35 U.S.C. §103(a).

35 U.S.C. §103(a)

All pending claims were rejected under 35 U.S.C. §103(a) as being unpatentable over Wierda and O'Brien, *Expert. Rev. Anticancer Ther.* (2001) 1:73-83 ("Wierda"); in view of Dmoszynska et al., *Leuk. Lymphoma* (1999) 34:335-340 ("Dmoszynska"); Denis-Mize et al., *J. Immunother.* (2003) 26:S43 ("Denis-Mize"); and further in view of U.S. Patent No. 4,518,584 to Mark et al. ("Mark"). The Office argues Wierda teaches a method for treating CLL using Campath-1H (Alelemtuzumab) thrice weekly up to 12 or 18 weeks. The Examiner correctly notes Wierda does not teach the combination of aldesleukin and Alemtuzumab, and the administration schemes presented in the dependent claims. Dmoszynska is cited for teaching administration of low dose IL-2 to induce an increase in T cell subsets and NK cells in CLL patients treated with the chemotherapeutic drug 2CdQ. Denise-Mize allegedly teaches the use of aldesleukin in combination with rituximab. Finally, Mark is cited as teaching that aldesleukin has a higher IL-2 activity than a native IL-2 control.

The Office asserts: "It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the humanized anti-cD52 antibody, Campath 1-H, taught by Wierda et al. with interleukin-2 taught by Dmoszynska et al or Denis-Mize for treating CLL..." Office Action, page 6. The Examiner also states with respect to the frequency, concentration and administration that "determination of optimum conditions is within the level of one of ordinary skill in the art." Office Action, page 7. However, applicants respectfully

disagree that the cited combination renders the present claims obvious.

In particular, Wierda is a review article describing various studies using chemotherapeutic and immunotherapeutic agents, such as Campath-1H. The Office acknowledges Wierda does not describe the use of aldesleukin and Alemtuzumab or the administration methods claimed in the present application. Additionally, Wierda does not relate to the use of concurrent combination therapy for treating CLL. Dmoszynska, like Wierda, also does not pertain to the use of concurrent combination therapy for treating CLL, as claimed. Rather, Dmoszynska relates to the use of IL-2 in patients previously treated with the chemotherapeutic agent 2 CdA. There is no discussion whatsoever regarding the use of IL-2 with antibody therapy. In fact, the only art cited that relates to combining IL-2 therapy with an antibody is Denis-Mize. However, this study used aldesleukin in combination with Rituximab. Alemtuzumab and Rituximab are completely different antibodies, directed against different surface antigens. In particular, Alemtuzumab is a humanized rat monoclonal antibody directed against human CD52, a 21-28 kDa phosphatidylinositolglycan-anchored glycoprotein. See, Wierda, page 76. Rituximab, on the other hand, is a humanized mouse monoclonal antibody directed against CD20, an unglycosylated protein. See, the accompanying Wikipedia description. Thus, the two antibodies are unrelated and the efficacy of substituting one antibody for the other is simply unpredictable. With respect to Mark, this patent merely describes the production of aldesleukin. The Examiner states that Table II of Mark shows that aldesleukin has higher biological activity than native IL-2, making it obvious to replace the IL-2 of Dmoszynska or Denis-Mize with that of Mark's. However, a review of Table II shows that the activity of aldesleukin is less than 10% higher, i.e., less than .1 times higher than the activity of native IL-2, hardly a significant difference.

Applicants' claims are directed to a new and nonobvious combination therapy for treating patients with CLL. Applicants submit this is not merely "optimization" that one of skill in the art achieved through "routine experimentation." One of skill in the art simply could not predict that a treatment regimen as claimed would indeed be efficacious. Cancer therapy is extremely complex and it is well known that the agents used and the dosing is critical.

It is also well known that combination therapy can lead to drug-drug interactions that have various effects. For example, there is always the possibility that one drug may alter the

intensity and pharmacological effects of another drug if given concurrently. The net result may be a non-existent or diminished effect of one or both of the agents, or the appearance of new effects not seen with either drug alone. For example, the interaction between the drugs may be pharmacokinetic, i.e., alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmadynamic, i.e., interactions between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with drugs that have serious toxicity and low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences. Drugs are known to interact at any point during their absorption, distribution, metabolism or excretion. Thus, the frequency of beneficial or adverse effects is unknown until the actual combination is tested. See, Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Publishing Division, 2001, pages 54-56, appended hereto for the Examiner's convenience. The teachings in this reference clearly support that the efficacy of two agents in combination, such as aldesleukin and Alemtuzumab, is unpredictable.

Accordingly, the combination cited by the Office does not provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions" (*KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007)) Rather, as explained above, the evidence is to the contrary.

For at least these reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

III. CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and request early notification to that effect. The Examiner is encouraged to contact the undersigned if the Examiner notes any further matters which might be resolved by a telephone interview.

Respectfully submitted,

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By: _____
Roberta L. Robins
Registration No. 33,208

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Telephone: 650-493-3400
Facsimile: 650-493-3440